

## REMARKS/ARGUMENTS

Favorable consideration of this application is respectfully requested in view of the above amendment and the following remarks.

Claims 34-42 are pending in the application. Claims 34-42 have been rejected. Claim 1 has been amended to recite specific autoclaving steps. Support for the additional language in amended Claim 1 can be found in the specification on page 5. No new matter has been added.

Claims 34-42 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 4,088,166 (Miller) in view of U.S. Patent 3,709,365 (Czaplinski et al.). In particular, the Examiner states on pages 2-3:

"Miller discloses a pharmaceutical package (col. 1, ll. 8-15), which comprises a closed polypropylene bottle/barrel (10) in which is disposed a solution as seen in Figure 1, wherein the solution does not fill the bottle completely and some air is disposed in the bottle (col. 6, ll. 11-22), a cap (32), a neck (14), the bottle has a bottom portion that has a concave configuration (22). Miller lacks after autoclaving the package at at least 121°C and for at least 20 minutes, suffers no deformation, does not shrink, and does not explode and where the package retains a sufficiently high squeezability to dispense the solution. Czaplinski et al. teach the use of autoclaving a polypropylene material at about 115° - 125°C from 20-30 minutes (col. 2, ll. 49-58).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize the teaching Czaplinski et al. onto Miller's package by autoclaving the package at at least 121°C, as taught by Czaplinski et al. in (col. 2, ll. 49-58), in order to treat a material that can withstand autoclaving at a temperature 121°C for at least 20 minutes."

Applicants respectfully disagree with the Examiner's conclusion and assert that the combined cited references do not make obvious the claimed subject matter as defined in amended independent Claim 34 for the reasons stated below.

At the outset, it is noted that the Examiner bears the initial burden of proving a *prima facie* case of obviousness. This burden can be met by showing some objective teaching in the prior art or that knowledge that is available to one of ordinary skill in the art would motivate that individual to combine the relevant teachings of the references. In re Fritch, 972 F.2d 1260, 1265, 23 U.S.P.Q. 2d 1780, 1783 (Fed. Cir. 1992) [citing In re Piasecki, 745 F.2d 1468, 1471-72, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984)]. The Applicant can rebut the Examiner's *prima facie* case of obviousness by showing it was improperly made out, or by providing objective evidence which supports a conclusion of non-obviousness. *Id.* at 1265 citing In re Heldt, 433 F.2d 808, 811, 167 U.S.P.Q. 676, 678 (CCPA 1970).

With particular relevance to the present application, MPEP §2141 (Basic Considerations Which Apply to Obviousness Rejections, a copy of which is attached hereto) states:

"When applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention...."

As demonstrated below, a *prima facie* case of obviousness has not been established. Before discussing the reasons for Applicants' conclusion, a brief summary of the presently claimed pharmaceutical package is set forth below.

The presently claimed pharmaceutical package as defined in amended independent Claim 34 comprises a closed polypropylene bottle in which is disposed a solution or gel comprising a pharmaceutical product. The solution or gel does not fill the bottle completely and some air is disposed in the bottle. The closed package is autoclaved by placing the closed package in an autoclaving chamber. The temperature and pressure in the chamber is adjusted as a function of time in accordance to the prerequisites of the material of the package, wherein a counter pressure is generated in the chamber and wherein the counter pressure is regulated electronically by computer control. The package, after autoclaving at at least 121°C for at least 20 minutes, suffers no deformation, does not shrink or explode and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel.

#### Reasons That a *Prima Facie* Case of Obviousness Has Not Been Established

1. Miller, when considered as a whole, fails to teach or suggest the presently claimed pharmaceutical package.

In considering the presently claimed pharmaceutical package and the teachings of Miller, the Examiner's attention is directed to MPEP §2141.02 (a copy of which is attached hereto) which indicates that when ascertaining the differences between the prior art and the claims at issue, not only must the claimed invention be considered as a whole, but also the prior art reference must be considered in its entirety, i.e., as a whole,...

In the present case, the Examiner has not considered the teachings pertaining to Miller's container in its entirety as is evidenced first by the Examiner's characterization of the Miller container as being:

"a closed polypropylene bottle/barrel (10) in which is disposed a solution as seen in Figure 1, wherein the solution does not fill the bottle completely and some air is disposed in the bottle (col. 6, ll. 11-22)..." and wherein after autoclaving "suffers no deformation, does not shrink, and does not explode and where the package retains a sufficiently high squeezability to dispense the solution."

When considering the teachings of Miller in its entirety, the container described in Miller is not a closed polypropylene bottle containing both a pharmaceutical solution and some air which upon autoclaving suffers no deformation, and retains a sufficiently high squeezability as is asserted by the Examiner. Instead, the container of Miller is a collapsible container (see column 1, lines 48-56, column 2 and Figures 4 and 5) that is made up of three different parts (see column 3, lines 7-12 and Figures 3-4):

- An integral neck portion (14) and shoulder portion (16) which are preferably relatively stiff; and
- the rest of the container (10) which is flexible and collapsible.

The complete structure of the container and an administration operation are described in Figures 1-6 and column 3, lines 7-18 wherein it states:

"Referring to the drawings, a molded, collapsible solution container (10) is disclosed which defines a body portion (12) having an integral neck portion (14) and shoulder portion (16) of one end thereof. Neck and shoulder portions (14, 16) are preferably relatively stiff, while the rest of the container is flexible and collapsible. Container (10) is sealed at its end (18) opposite the neck and shoulder portions (14, 16), and includes a flattened portion (20) having a hanger hole (22) so that the container may be hung up in the manner illustrated in FIG.1 for convenient administration of parenteral solution or any other material as desired.

FIG. 1 schematically shows such an administration operation, in which an administration set (23), conventionally including a drip chamber (24) and flexible tubing (26), connects the interior of container (10) with an infusion needle (28) in the arm of a patient, for flow of parenteral solution from container (10) to an arm vein in a manner controlled by flow clamp (30)."

Indeed, Miller throughout makes clear that the container is specifically designed to be collapsible. For example, the paragraph bridging column 1 and column 2, states:

"In accordance with this invention, gusset portions are defined in the body portion adjacent the shoulder portion. The gusset portions include lines of flexing weakness to facilitate the collapse of the container adjacent the shoulder portion as the contents thereof are withdrawn, typically through the neck portion while the container is disposed in neck-downward position. In these circumstances, the gussets can facilitate both the lateral and longitudinal collapse of the container as it is emptied." [emphasis added by underlining]

In particular with respect to the gusset structure, Miller at column 5, lines 50-59 states:

"The gusset structure permits the further collapse under normal suction pressure of the type exerted within the container due to the weight of the solution in administration set (26) and the normal elevation for the container as used. The container collapses both longitudinally and laterally in the region of gusset (68), adjacent shoulder (16), which further reduces the volume of the collapsed container, and permits the expulsion of more parenteral solution. This is particularly illustrated by FIGS. 6A and 9, when compared with FIGS. 5 and 8."

Miller also indicates that it is preferred that the circumferences of the transverse cross-sections defined by a major portion of the length of the container are essentially constant which also facilitates the collapse of the container (see column 2, lines 9-14). Miller further indicates that a pair of longitudinal lines of flexing weakness (58) are defined along both lateral container edges that further facilitate the flat collapse of the container (see column 2, lines 21-26 and column 5, lines 3-6.).

Miller also indicates that as the contents are withdrawn from the inverted container, the container collapses in a uniform manner to permit the accurate measurement of the amount of the solution withdrawn from the container (see column 4, lines 34-40 and column 6, lines 16-20).

Accordingly, Miller throughout emphasizes that the container when considered as a whole is specifically designed to be collapsible, particularly to determine how much parenteral solution has been expended from the container. Accordingly, the solution container does not retain sufficient squeezability as is asserted by the Examiner.

In contrast to the collapsible solution container of Miller, the presently claimed pharmaceutical package comprising a closed polypropylene bottle containing the solution or gel comprising a pharmaceutical product, upon autoclaving does not deform and retains a sufficiently high squeezability to dispense the solution or gel.

While Miller states that the filled solution container can be autoclaved, the fact remains that the Miller container is designed to collapse for the purpose of determining the amount of solution expended from the container. Miller is not concerned with solving the problem of autoclaving a pharmaceutical package so that it still retains a sufficient squeezability to dispense one drop at a time a solution or gel containing a pharmaceutical product. In addition, Miller is not concerned with the problem of whether the container will shrink or explode upon autoclaving.

Miller also does not teach or specifically suggest that such a closed filled bottle is autoclaved by the process as recited in steps (a) and (b) of amended independent Claim 1.

Since Miller when considered in its entirety, describes a solution container that is specifically designed to be collapsible for a completely different purpose from the presently claimed pharmaceutical package, and Miller does not describe the particular steps utilized to autoclave such a package, it can be fairly stated that Miller fails to teach or specifically suggest the presently claimed pharmaceutical package as set forth in amended independent Claim 34.

Further, even assuming *arguendo* the Examiner were to assert that it would be obvious to modify the Miller container to arrive at the presently claimed pharmaceutical package, it is asserted that such modifications would not be obvious. The Federal Court on the issue of obvious 'modifications' has instructed that:

"The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."

*Id.* at Page 1226 [citing In re Gordon, 733 F.2d at 902, 221 U.S.P.Q. at 1127]

In the present case as stated above, there is no teaching or specific suggestion to modify the structure of the collapsible solution container in Miller to a pharmaceutical package comprising a polypropylene bottle which upon being autoclaved has retained a sufficiently high squeezability to dispense one drop at a time a solution or gel comprising a pharmaceutical product as set forth in amended Claim 34. Further, there is no concern in Miller to solve the problems associated with autoclaving such a pharmaceutical package so that it suffers no deformation or shrinkage and still retains a sufficient squeezability to dispense one drop at a time a solution or gel containing the product. Accordingly, Miller fails to suggest the desirability of such a modification.

Indeed, if the Miller's collapsible container was modified to the presently claimed pharmaceutical package comprising a polypropylene bottle suffering no deformation or shrinkage and retaining a sufficiently high squeezability, the modified container would arguably be rendered unsatisfactory for the purpose of accurately measuring the amount of solution expended from the container. With regard to modifying the prior art invention to arrive at the claimed invention, the Federal Court has held that if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984).

- 2) Miller teaches away from the presently claimed pharmaceutical package by teaching a solution container that is specifically designed to be collapsible.

It is well settled that a determination of obviousness not only requires that the claimed invention be read as a whole, but also that the prior art reference be read as a whole and that:

"consideration must be given where the references diverge and teach away from the claimed invention."

Akzo N.V. v. United States Intl Trade Commission, 808 F.2d 1471, 1481, 1 U.S.P.Q. 2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987).

The Federal Court has instructed that a prior art reference "teaches away" when one of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the prior art reference, or alternatively, would be led in a direction divergent from the path that was taken by the applicant. In re Gurley, 31 U.S.P.Q. 2d 1131 (Fed. Cir. 1994).

In view of the above instruction, it can fairly be said that Miller, in teaching a solution container that is specifically designed to be collapsible, i.e., a container that arguably would suffer deformation and loss of sufficient squeezability, specifically teaches away from the presently claimed pharmaceutical package comprised of a closed polypropylene bottle which suffers no deformation and which retains sufficiently high squeezability such that it can easily dispense one drop at a time the solution or gel comprising the pharmaceutical product. Accordingly, one skilled in the art armed with the teaching of Miller would be led in a direction divergent from the path that was taken by the Applicants, that is, one skilled in the art would not have chosen to construct a pharmaceutical package that upon being autoclaved retains sufficient squeezability to repeatedly dispense one drop at a time a solution or gel containing a pharmaceutical product.

- 3) The teachings of Czaplinski et al. when considered as a whole and combined with Miller fail to teach or specifically suggest the presently claimed pharmaceutical package, and thus fail to suggest the desirability of and thus the obviousness of combining Miller with Czaplinski et al.

Czaplinski et al. describe a radioactive generator system having a sterile, sealed disposable closure therein. As shown and described in Figure 1 and column 2, lines 3-62 of Czaplinski et al., the generator system (4) is connected to an elution bottle (12) containing an elution solution (10) via a hypodermic needle. The details of the generator system (4) are more fully set out in U.S. Patent 3,369,121 (Bruno et al., a copy of which is attached) which is referenced in Czaplinski et al. (see column 2, lines 9-11). As described in Bruno et al., the generator system houses a column which has bound to it radioactive material (see columns 2 and 3). As further described in Bruno et al. (see

column 3, lines 62-75), the column, prior to its insertion in the generator system, is filled with a radioactive solution. Most of the radioactive material is absorbed onto the column and the excess radioactive material and water pass through the column and are removed. The column is then washed with acid and saline to remove any non-absorbed radioactivity and the column is sterilized, as by autoclaving. Following autoclaving, the sterilized column containing the bound radioactive material is inserted into the body of the generator.

As further described in Czaplinski et al. (see column 2, lines 3-62), the eluting solution contained in the elution bottle which is hooked up to the generator system flows through the sterilized column of the generator system and the eluate containing the radioactive material is removed via a hypodermic needle from the bottom of the generator system and allowed to pass through conduit (22) into sterile closure (30) and then through conduit (24) into vial (20).

The sterile closure (30) comprises *inter alia*, a housing (42) wherein one end is closed by a pierceable membrane and the opposite end remains open, a membrane filter placed between the membrane and the open end, and a seal around the closed end of the housing (42) to retain the membrane in position. The purpose of the sterile closure (30) is to ensure sterility at the site of delivery of the radioactive material and reduce contamination of the generator system (see Czaplinski et al., column 1, lines 41-50).

While Czaplinski et al. (see column 2, lines 49-55) indicate that the housing material (42) can be made of a plastic, e.g., polypropylene or metal material which withstands autoclaving, e.g., about 115-125°C, it is apparent from reading Czaplinski et al., that the sterile closure (30) comprising *inter alia* the housing material (42) made of plastic or metal is sterilized prior to being connected to conduits (22) and (24) to ensure sterility at the site of delivery of the radioactive material. Importantly, Czaplinski makes clear that the radioactive material eluting from the column has already been sterilized prior to its elution from the column and is not sterilized at 115-125°C when it passes through the housing material (42) of the sterile closure (30). Thus, the radioactive material eluted from the column is not contained in the closure (30) when the closure (30) was previously sterilized. Accordingly, Czaplinski et al. fail to teach or specifically suggest autoclaving a pharmaceutical package comprising a closed polypropylene bottle which has disposed a solution or gel comprising a pharmaceutical product and air. Czaplinski et al., also fails to teach or specifically suggest that such a pharmaceutical package suffers no deformation and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel. As stated above, Czaplinski et al. is merely concerned with the problem of ensuring sterility at the site of delivery of the radioactive material and to

reduce contamination of the generator system. Accordingly, Czaplinski et al., as a whole, does not teach or suggest the presently claimed pharmaceutical package.

In sum, Miller, as a whole, teaches a collapsible solution container and is deficient *inter alia* in teaching that the dispenser when autoclaved suffers no deformation or shrinkage and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel comprising a pharmaceutical product. In addition, Miller, teaches away from the presently claimed pharmaceutical package, by teaching a container that is specifically designed to collapse, which collapsed container would arguably suffer deformation and would not retain a sufficiently high squeezability. Further, if the Miller collapsible container was modified to the presently claimed pharmaceutical package, the modification would arguably render the dispenser inoperable for its intended purpose, i.e., to accurately determine the amount of solution expended from the container.

Czaplinski et al., as a whole, while describing a radioactive generator system, which system *inter alia* includes a housing material made of plastic, the housing material is actually autoclaved prior to placement between conduits (22) and (24) of the generator system, and thus the radioactive solution is not contained in the housing material upon autoclavation. Accordingly, Czaplinski et al. is deficient in teaching or suggesting the elements missing from Miller, i.e., a closed polypropylene bottle which is disposed a solution or gel and some air, which upon autoclaving suffers no deformation and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel.

Accordingly, it is difficult to see how Miller and Czaplinski et al. when viewed as a whole suggest the desirability of and thus the obviousness of combining Miller and Czaplinski et al. to arrive at the presently claimed invention as defined in Claim 34.

4) The §103 rejection is based on hindsight reconstruction.

It is respectfully submitted that the Examiner is relying upon hindsight to arrive at the determination of obviousness by picking and choosing separate components of the prior art references and using them to piece together the claimed subject matter without evaluating the references as a whole. The Federal Circuit has held that:

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination....The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

It is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

In re Fritch, 23 U.S.P.Q. 1781, 1783, 1784 (Fed. Cir. 1992).

Indeed, the Federal Circuit has repeatedly cautioned against using hindsight by using the Applicants' disclosure as a blueprint to reconstruct the claimed subject matter out of isolated teachings from the prior art. See also Grain Processing Corp. V. American Maize-Products Co., 840 F.2d 902, 5 U.S.P.Q. 2d 1788 (Fed. Cir. 1988).

Since as discussed above, 1) Miller fails to teach or suggest a pharmaceutical package comprising a closed polypropylene bottle which is disposed both a solution or gel and air, wherein the bottle upon autoclaving suffers no deformation or shrinkage and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel; 2) Miller fails to teach or suggest the steps of the autoclaving process, i.e., steps (a) and (b), of Claim 1 for such a package, 3) Miller teaches away from a pharmaceutical package which when autoclaved suffers no deformation and retains sufficient squeezability to dispense one drop at a time a solution or gel containing pharmaceutical product; and 4) Czaplinski et al. fail to teach the elements that are deficient in Miller, it is clear that the Examiner has used hindsight to pick and choose among the isolated disclosures of the prior art to deprecate the present claims.

Accordingly, Miller and Czaplinski et al., each taken alone or combined, do not make obvious the pharmaceutical package defined in amended independent Claim 34.

In view of the above, withdrawal of the rejection of Claims 34-42 under 35 U.S.C. §103(a) is respectfully requested.

Claims 36-40 and 42 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Miller in view of Czaplinski as applied to claim 35 above, and further in view of EP0322134 (Carter). In particular, the Examiner stated *inter alia*:

"Miller-Czaplinski et al. in combination have taught all the features of the claimed invention except that the cap being threaded onto the neck. Carter teaches the use of a container (20), threaded neck (26b) and a threaded cap (22).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize Carter's teaching onto the neck of Miller and Czaplinski et al. in order to provide an alternate means of attaching the cap onto the container neck for tight sealing."

Applicants respectfully disagree with the Examiner's conclusion and assert that the combination of Miller, Czaplinski et al. and Carter et al. does not make obvious Claims 36-40 and 42 for the reasons stated below.

With respect to Miller and Czaplinski et al., Applicants reiterate the arguments proffered to address the §103(a) rejection above, namely that 1) Miller fails to teach or suggest a pharmaceutical package comprising a closed polypropylene bottle which is disposed both a solution or gel and air, wherein the bottle upon autoclaving suffers no deformation or shrinkage and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel; 2) Miller fails to teach or suggest the autoclaving process, i.e., steps (a) and (b), of Claim 1 for such a package; 3) Miller teaches away from a pharmaceutical package which when autoclaved suffers no deformation and retains sufficient squeezability to dispense one drop at a time a solution or gel comprising pharmaceutical product; and 4) Czaplinski et al. fails to teach the elements that are deficient in Miller.

Carter is also directed to a method of packaging and sterilizing a pharmaceutical product. In particular, Carter describes a process for sterilizing a polypropylene bottle containing a saline solution. Carter, however, makes clear that the bottle must be filled to the maximum point to eliminate air being trapped in the bottle. (see column 4, lines 49-59). Indeed, Carter indicates that air being trapped in the bottle is a problem, because the trapped air will expand and produce a pressure that is greater than the pressure created during autoclaving. Carter further indicates that the pressure causes expansion of the softened polypropylene bottle, such that when the bottle cools dimples form in the expanded areas of the bottle. Accordingly, Carter et al. does not teach or specifically suggest a closed polypropylene bottle in which is disposed a solution or gel comprising a pharmaceutical product, wherein the solution or gel does not fill the bottle completely and some air is disposed in the bottle as set forth in amended Claim 1. In addition, Carter et al. does not teach or suggest autoclaving such a bottle by steps (a) and (b) as recited in amended Claim 1. Further, Carter teaches away from the present invention by indicating that air should be eliminated from the bottle because the air in the bottle when the bottle is autoclaved can cause dimpling of the bottle. Thus, one skilled in the art would be discouraged from utilizing Carter to arrive at the presently claimed invention. Accordingly, the combination of Miller, Czaplinski et al. and Carter does not make obvious Claims 36-40 and 42.

In view of the above, withdrawal of the rejection of Claims 36-40 and 42 under 35 U.S.C. 103(a) is respectfully requested.

The Examiner has also indicated that the prior art made of record and not relied on, U.S. Patent 6,129,925 (Kido et al.) and U.S. Patent 3,826,059 (Novitch), is considered pertinent to Applicants' disclosure.

Kido is directed to an infusion preparation set (a container filled with infusion liquids) useful for preparing a stable infusion liquid containing sugars, amino acids, electrolytes, a fat emulsion and vitamins. Kido solves the problem of preparing a stable infusion liquid by putting

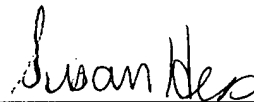
the infusion liquid containing a fat emulsion and sugars into the first compartment of a container having two compartments which are separated by a separation means, putting an infusion liquid containing amino acids and electrolytes into its second compartment, sterilizing the container, preserving it in this state, and mixing the infusion liquids contained in the first compartment and the second compartment by removing the separation means upon use. There is no teaching or suggestion that the container upon autoclaving suffers no deformation, does not shrink and that the container retain a sufficiently high squeezability to dispense one drop at a time the solution or gel comprising a pharmaceutical product. Accordingly, Kido does not anticipate or render obvious the present invention as defined in Claim 34.

Novitch is directed to a dually sealable, non-leaking vial for shipping radioactive materials. There is no teaching or specific suggestion in Novitch of a polypropylene bottle nor the requirements that such a bottle upon autoclaving does not suffer deformation and retains a sufficiently high squeezability to dispense one drop at a time the solution or gel comprising a pharmaceutical product. Accordingly, Novitch does not anticipate or render obvious the present invention as defined in Claim 34.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below.

Respectfully submitted,

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Date: October 13, 2005